REMARKS

Claims 23-43 are now pending in the application and claims 31-43 are new. The Examiner is respectfully requested to reconsider and withdraw the rejections in view of the amendments and remarks contained herein.

1. TELEPHONIC INTERVIEW WITH EXAMINER

Applicant's representative thanks Examiner Zohreh A. Fay for the opportunity, dialogue, and time invested in the telephonic interview conducted on July 24, 2007. The interview provided the chance to further describe features and benefits of the present invention as compared to the art of record. Although no agreement was reached regarding the present rejections, Applicant's representative appreciates the discussion regarding the pending claims and cited references. As such, it is believed the remarks submitted in this reply illustrate the patentability of the present claims and effectively address the Examiner's concerns with the Viegas and Chang references.

2. BACKGROUND AND SUMMARY OF CLAIMS

The present invention is drawn to methods for preservation and treatment against bacterial infection and inflammation in an ophthalmological surgery site. The claimed methods include an applying step where a pharmaceutical composition containing both a viscoelastic substance and an antimicrobial agent is made to directly contact an anterior chamber, endothelium of cornea, lens capsule and a passage of aqueous humor. See independent claim 23; and paragraphs [0026] to [0043]. The method may be used to prevent infection in cataract or glaucoma surgery and the pharmaceutical composition in the applying step may further include an anti-inflammatory agent. See claims 26, 27, and 30; paragraphs [0048] and [0052]; and Example 2, including paragraphs [0093] to [0095]. Embodiments also include the step of

removing the pharmaceutical composition from the intraocular site, wherein residual traces of the pharmaceutical composition exhibit at least one of an antimicrobial effect and an antimycotic effect. See independent claims 31 and 39. As a result, the present invention can prevent infection within the intraocular cavity of the eye and may further inhibit post-surgical inflammation. Paragraphs [0051] and [0096].

2.1 A viscoelastic substance is used during cataract surgery.

In cataract surgery, one goal is to prevent the anterior chamber of the eyeball from collapsing. See paragraph [0048]. For example, when the closed cavity of the eyeball is dissected, the aqueous humor can flow out form the anterior chamber due to inner pressure, whereby the eyeball may consequently collapse. A viscoelastic substance can be placed within the intraocular cavity to prevent the eye from collapsing. See paragraph [0048]. Likewise, implantation of an artificial lens requires creation of a space to receive the lens within the intraocular cavity. The viscoelastic composition can be used to form the necessary intraocular space for lens implantation. See paragraph [0048].

2.2 Residual traces of the viscoelastic substance persist following surgery.

The viscoelastic substance is typically removed after surgery; however, it is impossible to remove all traces of the substance from the intraocular cavity. See paragraphs [0010] and [0091]. The substance may be slightly decomposed by intraocular enzymes but is mostly discharged outside the eye with the aqueous humor flowing out from the anterior chamber. See paragraph [0010]. For example, the substance may remain in the eye with a half-life of four hours. See paragraph [0010].

2.3 The surgery and/or viscoelastic substance can introduce exogenous bacteria.

The intraocular cavity is typically aseptic but can be contaminated with exogenous bacteria which enter from outside during the surgery. See paragraphs [0009] and [0053]. Conventionally, a viscoelastic substance for insertion into the intraocular cavity is used to

prevent collapse, and in order to prevent infection, a separate antimicrobial agent is used. The antimicrobial is typically administered either systemically via oral intake or intravenous drip or locally via an ophthalmic solution or intraocular injection. See paragraphs [0011] and [0052].

2.4 The present invention addresses issues of microbial infection in new and advantageous ways.

Applicant has identified heretofore unappreciated modes of action relating to infection and in formulating the present invention has overcome problems with the conventional methods. Applicant has noted that the viscoelastic substance seems to inhibit the normal self-cleansing activity of the aqueous humor to flush out any introduced bacteria, thereby permitting or increasing the risk of infection. See paragraphs [0025] and [0091]. The residual traces of a typical viscoelastic substance can potentially harbor and/or shield exogenously introduced bacteria from an antimicrobial, consequently preventing systemically administered or separately injected antimicrobial agents from contacting the bacterial.

Applicant's claimed invention as overcomes these problems. By mixing an antimicrobial agent with the viscoelastic substance, bacterial infection can be prevented or treated within the intraocular cavity of the eye at the location of the residual traces of material. See paragraph [0052]. Thus, the claimed methods prevent bacteria from eluding physiological disinfection and sterilization caused by the traces of viscoelastic substance that remain after surgery. See paragraph [0052]. The antimicrobial agent can therefore act at the most requisite time and site. See paragraph [0096].

3. REJECTION UNDER 35 U.S.C. § 102

Claims 23, 24 and 26 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Viegas et al. (U.S. Pat. No. 5,587,175). This rejection is respectfully traversed.

The present claims include, among other features, applying a composition of a viscoelastic substance and antimicrobial agent so that it directly contacts an anterior chamber, endothelium of cornea, lens capsule, and a passage of aqueous humor. See independent claim 1. Therefore, the claims expressly apply the composition to an intraocular space (i.e., inside the eyeball). Additional methods include application of the composition in cataract surgery or glaucoma surgery, procedures in which the composition can be used to prevent collapse of the anterior chamber, for example. See claims 27, 33, 37, and 39; and see paragraph [0048]. Other embodiments include a step of removing the pharmaceutical composition from the intraocular site, wherein residual traces of the pharmaceutical composition exhibit at least one of an antimicrobial effect and an antimycotic effect. See independent claims 31 and 39.

3.1 The only ophthalmic-based teachings in Viegas relate to external applications; i.e., corneal shields and masks

In contrast to the present invention, the Viegas reference only teaches topical application to the eyeball, including processes employing protective corneal shields or laser ablatable masks **to cover the outside of the eye**. See Viegas col. 1, lines 11-15. The reference does not teach any process or method where the composition is applied to an intraocular space (i.e., within the eye) and therefore cannot anticipate the present claims. See *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987) (Each and every element as set forth in the claim must be present in the reference for the claim to be anticipated.). For example, there is no disclosure of internal ophthalmological applications such as cataract or glaucoma surgeries. The injection or body cavity applications taught in Viegas are disclosed only as alternate embodiments, where the gel serves as a drug depot or to separate organs during a surgical procedure in order to prevent adhesions. See Viegas col. 4, line 57 to col. 5, line 6. In addition, nowhere does Viegas teach removal the gel composition.

Viegas is completely silent regarding any process or method employing a viscoelastic substance to prevent collapse of an intraocular space such as the anterior chamber. Instead, Viegas is focused on matching pH and osmolality of the eye and preventing loss of the drug delivery composition due to lacrimal drainage (i.e., the flushing action of tears) released between the eyelids and the eyeball (i.e., the exterior of the eyeball). See Viegas col. 8, lines 37-57. These benefits are applicable to corneal shields and masks to protect and hydrate the eye during excimer laser keratectomy, for example. See Viegas Examples 11-15. As such, all processes relating to composition delivery to the eye taught in Viegas are in reference to exterior applications (e.g., corneal shields or masks). See Viegas abstract; col. 1, lines 11-15; col. 4, line 67 to col. 5, line 2; col. 9, lines 15-31; col. 10, lines 63-67; and Examples 1-5 and 11-15.

3.2 The Viegas teachings do not support the present rejection – Viegas teaches topical ophthalmic uses *or* injection to a body cavity, not an eye.

It is alleged on Page 2 of Office Action from September 11, 2006 that Viegas teaches use of the disclosed composition in a body cavity or by injection. The Examiner cites the Viegas abstract; col. 4, lines 56-60; col. 6, lines 48-65; and Examples 1, 2, and 5 as support. However, **none of the cited passages of the Viegas reference teaches applying the composition to the intraocular space or using the composition in cataract or glaucoma surgeries**. And notably, when viewing the reference teachings as a whole, it is clear that application to a body cavity by injection is separate from application to the cornea of the eyeball, as these features of Viegas are set out separately and are not coextensive.

First, regarding the Viegas abstract as cited by the Examiner, the gel is said to be suited for topical body cavity or injection application; for delivery to the eye of a mammal; as a protective corneal shield; or as an ablatable corneal mask. These various uses are all presented in the alternative; none are examples of each other. Thus, the Viegas abstract

differentiates between injection application and various uses for the eye. Nowhere in the abstract, or the whole Viegas reference for that matter, is there any disclosure regarding injection within the eye to an intraocular space.

Second, regarding col. 4, lines 56-60 as cited by the Examiner, the reference discloses processes that include topical, injection, or body cavity delivery. Viegas col. 4, lines 57-59. These are recited in the alternative and are therefore mutually exclusive. Notably, in the subsequent lines, the only embodiments involving the eyeball include a protective corneal shield and an ablatable corneal mask, which are examples of topical uses. Viegas col. 4, line 67 to col. 5, line 2. Consequently, this portion of the reference fails to disclose applying the gel to the interior of the eyeball.

Third, regarding col. 6, lines 48-65 as cited by the Examiner, these passages simply describe various water-soluble, film-forming polymers. There is no disclosure of using these polymers within the intraocular space.

Fourth, regarding Examples 1, 2, and 5 as cited by the Examiner, these three embodiments each teach a laser ablatable corneal mask or protective corneal shield, which are all surface (cornea) applications. In fact, these examples serve to exemplify that Viegas only contemplates use of the disclosed compositions **in external applications to the eye**. Nowhere does the reference ever describe a method that includes applying the composition to the anterior chamber, cornea endothelium, lens capsule, and passage of aqueous humor.

3.3 Viegas is silent regarding removal of the gel composition.

Independent claims 31 and 39, and their corresponding dependent claims, include the step of removing the pharmaceutical composition from the intraocular site, wherein residual traces of the pharmaceutical composition exhibit at least one of an antimicrobial effect and an antimycotic effect. Viegas is silent regarding any teaching that involves removing the gel

composition. As such, these claims are further distinguished over Viegas and cannot be anticipated by the reference.

3.4 Viegas does not teach all the features of the present claims and is not an anticipatory reference.

In sum, the Viegas reference teaches injection of gel compositions for the separation of organs and prevention of undesirable adhesions. Viegas col. 5, lines 3-5. Whereas all teaching and description relating to uses for the eye includes topical application to the cornea. No disclosure or examples are provided relating to intraocular methods or surgeries, such as cataract or glaucoma treatments as found in Applicant's claims. Accordingly, the Viegas reference cannot anticipate claims 23-43. Applicant respectfully requests reconsideration of the claims and withdrawal of the rejection.

4. REJECTION UNDER 35 U.S.C. § 103

Claims 25 and 27-30 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Viegas et al. (U.S. Pat. No. 5,587,175) in view of Chang (U.S. Pat. No. 6,051,560). This rejection is respectfully traversed.

As described in the preceding sections, the present claims are drawn to methods that apply a viscoelastic substance including an antimicrobial agent to an intraocular space of the eyeball. The viscoelastic substance may further include an anti-inflammatory and the methods may be employed in cataract and glaucoma surgeries. See claims 27 and 30. The methods prevent bacterial infection within the eye since residual traces of the viscoelastic substance remaining in an intraocular space present the antimicrobial agent to any exogenously introduced bacteria contacting the viscoelastic substance. The present methods are advantageous compared to separate systemic or local administration of antibiotic, since the viscoelastic substance can prevent penetration of a separate antibiotic, effectively shielding bacteria and

allowing infection to occur. Moreover, the optional anti-inflammatory agent can prevent inflammation associated with bacterial infection.

4.1 No reason exists by which to combine Viegas and Chang.

The combination of Viegas and Chang cannot render the presently claimed methods obvious as there is no apparent reason evident in the references themselves or based on the general knowledge in the art by which a skilled artisan would combine their teachings as alleged. The Viegas gel composition is only applied as external corneal masks or shields while the Chang composition is disclosed in methods that simply maintain spatial separation of the cornea endothelium (i.e., the lumen or interior side of the cornea). Neither reference appreciates the issues regarding exogenous bacterial infection within an intraocular space that are addressed by the present invention. Only Applicant's methods afford antimicrobial properties to residual traces of viscoelastic substance left within the eyeball, which consequently do not shield bacteria from the antimicrobial agent as is the case with separately administered antibiotics.

To establish a *prima facie* case of obviousness, the prior art references must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). In addition, there must be some apparent reason either in the reference or the general knowledge in the art to combine or modify the references to include the missing subject matter. See *Id.*, and *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. ___, 2007 WL 1237837, at *14 (2007). The apparent reason to combine or modify the references should be made explicit in order to facilitate review. *Id.*; and see *In re Kahn*, 441 F3d 977, 988 (Fed. Cir. 2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning to support the legal conclusion of obviousness.").

In this case, the Viegas and Chang references are devoid of any reason or motivation to apply a viscoelastic substance having an antimicrobial agent to an intraocular space. On one

hand, Viegas teaches a process using a gel composition having an antibacterial substance as a corneal mask or shield to protect the cornea exterior during excimer laser keratectomy; e.g., Viegas Examples 11-15. On the other hand, Chang teaches high viscosity compositions used to maintain the corneal dome and protect corneal endothelial cells during intraocular lens implantation surgery. See Chang col. 1, lines 58-65; lines 30-33; and lines 45-50. However, there is no basis or support for a skilled artisan to combine their teachings found within the references and no reason based on the general knowledge in the art is provided as a nexus to combine these two references. Nothing in either reference speaks to the desirability of using the Viegas gel composition within an intraocular space as per the Chang composition.

4.2 Motivation to combine requires showing desirability of the combination, not merely piecing together the claimed invention based on Applicant's disclosure.

The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). In this case, neither reference appreciates that residual traces of viscoelastic substance can harbor exogenous bacterial within the eye and which can further block access of separately administered antibiotics. Both Viegas and Chang fail to recognize the problems and connections between bacterial infection and traces of viscoelastic substance left behind following intraocular surgery. Only the present invention and claimed methods apply a viscoelastic substance having an antimicrobial agent to an interior portion of the eye. The present inventive methods can prevent infection and do not shield or block antibiotic from reaching exogenously introduced bacteria, as is the case with a separately administered antimicrobial. Consequently, the present claims are not obvious since nether reference identifies why it may be desirable to combine the respective teachings in the manner alleged.

Finally, determination of obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention. There must be a teaching or suggestion within the prior art, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources of information, to select particular elements, and to combine them in the way they were combined by the inventor. *ATD Corporation v. Lydall, Inc.*, 159 F.3d 534, 48 USPQ2d 1321, 1329 (Fed. Cir. 1998). Since these references do not indicate why the alleged combination is desirable or provide an apparent reason to selectively combine their teachings, the present claims are not obvious. And if a reason exists in the general knowledge in the art, the Examiner has failed to identify such in the present rejection and consequently has failed to provide the explicit analysis required by an obviousness inquiry.

4.3 Obviousness requires that the combination teach all the claimed features.

To establish a *prima facie* case of obviousness, the prior art reference must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). In this case, independent claims 31 and 39, including their respective dependent claims, expressly include the step of removing the pharmaceutical composition, wherein traces of the pharmaceutical composition remain in the anterior chamber and the traces of the pharmaceutical composition provide an antimicrobial effect, antimycotic effect, and/or anti-inflammatory effect. The Viegas and Chang references are silent regarding removal of their respective gels or compositions following intraocular application. Consequently, claims 31-43 are not obvious.

4.4 Secondary considerations demonstrate the effectiveness and advantages of the claimed methods versus conventional methods.

Applicant further points to Exhibits A, B, C, and D that were provided with the Amendment filed February 12, 2007 as evidence of secondary considerations that distinguish

the present claims versus convention methods used in ophthalmic surgery. The present invention and claims include methods that are recognized by Applicant's peers as important developments in treating microbial infections incident to ophthalmic surgery. For example, Exhibit A illustrates accolades received from the Japanese Ophthalmic Society. Exhibits B and C illustrate peer-reviewed journal publications that describe how viscoelastic material can decrease antibacterial action, but when the antibacterial is mixed with the viscoelastic material superior prevention of infection can result. Finally, Exhibit D shows the effect of adding an antibacterial agent, either separate from the viscoelastic substance or mixed with viscoelastic substance, after the eye is presented with a bacterial challenge. Separate application of the antibacterial agent and viscoelastic material resulted in persistent infection, while application of mixed antibacterial and viscoelastic material significantly reduced the number of positive infections. See also Exhibit C.

These Exhibits touch on several important Graham Factors, namely unexpected results, long-felt need, and failure of others. See *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). In particular, the Exhibits contrast the success of Applicant's invention and claims versus the unsatisfactory results or failure of conventional methods that apply a viscoelastic substance and separately apply an antimicrobial agent. In view of the conventional methods, it is unexpected that mixing the antimicrobial with the viscoelastic substance would be better than applying these components separately. The conventional methods failed to appreciate and recognize that the viscoelastic substance can shield or block the separate antimicrobial from contacting bacteria. Moreover, the conventional methods did not appreciate that residual traces of viscoelastic material can persist in the eye after substantially all the material is removed. By mixing antimicrobial with viscoelastic substance, the antimicrobial agent can therefore act at the most requisite time and site and suppress bacteria associated or in contact with the residual

traces of material. Consequently, Applicant's invention addresses a long-felt need to prevent ocular infections and overcomes the failures associated with conventional methods.

In view of the preceding remarks, Applicant respectfully requests reconsideration of the claims and withdrawal of the rejection.

5. CONCLUSION

It is believed that all of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the outstanding Office Action and the present application is in condition for allowance. Thus, prompt and favorable consideration of this amendment is respectfully requested. If the Examiner believes that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (248) 641-1600.

Respectfully submitted,

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